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THE COMPOSITION OF MODERN QUINETUM

By JOHN AUGUSTUS GOODSON and THOMAS ANDERSON HENRY

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According to Dymock, Hooper and Warden¹ "quinetum" or "cinchona febrifuge" originated in the following way:—

"At the suggestion of Dr. J. E. de Vrij the manufacture of a light coloured powder, consisting of the alkaloids of red bark (i.e. bark of *Cinchona succirubra*) was started in 1874. This powder was called 'quinetum' or 'febrifuge' or with reference to the locality of its product Sikkim or Darjeeling febrifuge."

The gradual change in the nature of this material in India is thus described by Colonel Gage²:—

"So, in 1874, Cinchona febrifuge—being a mixture of the total alkaloids of *C. succirubra*—began to be manufactured, and from then until 1887 was the sole product of the Indian factories. About the same time the policy of replacing *C. succirubra* on the plantations by the quinine-yielding species was begun, but it was not until 1887, or about sixteen years after the introduction of cinchona into India, that it was found possible to start the manufacture of quinine in that country.

"By 1903, the scarcity of *C. succirubra* trees led to an alteration in the process of manufacture of cinchona febrifuge.

From that year it has consisted of a mixture of the residual alkaloids remaining after the extraction of quinine from the barks of *C. Ledgeriana* and its hybrid with *C. succirubra*, a certain amount of quinine being added to the mixture to make it approximately similar to the original febrifuge made from *C. succirubra*."

Although "quinetum" proper thus deteriorated into the inferior product, now known as "cinchona febrifuge," the composition of which has been dealt with in a previous paper,³ "quinetum" has never quite disappeared, and is still in fact regularly manufactured. In view of attempts to revive interest in the use of mixtures of cinchona alkaloids for the treatment of indigent malarial populations, it seemed desirable to examine the "quinetum" now available in commerce.

The three samples of "quinetum" used were ordinary commercial samples obtained from manufacturers in three different countries.

No. 1 consisted of a colourless powder completely and readily soluble in dilute sulphuric acid.

No. 2 was a pale, stone-coloured powder, which left about 3 per cent. of colourless inorganic matter undissolved by dilute sulphuric acid.

No. 3 was a pale brown powder, completely soluble in dilute sulphuric acid.

The samples were analysed by Chick's method,⁴ with the exception that the quinine and cinchonidine were precipitated together as dextrotartrates and the proportions of the two alkaloids in the precipitate calculated from the results of a methoxyl determination on the mixed bases recovered from the tartrate precipitate.

The results, including the usual corrections for solubilities, were as follows:—

TABLE I

	Sample 1 per cent.	Sample 2 per cent.	Sample 3 per cent.
Quinine	32.1	18.5	14.7
Cinchonidine	36.9	25.7	10.9
Quinidine	0.4	3.2	3.8
Cinchonine	30.9	48.9	44.7
Amorphous alkaloids*	nil	nil	12.7
Moisture	0.7	1.0	1.7
Ash	1.0	4.6	1.8

* Throughout this paper "amorphous alkaloids" means "ether-soluble amorphous alkaloids."

It was pointed out in a previous paper³ that the methoxyl method of determining quinine in a mixture of quinine and cinchonidine bases did not always give results agreeing with those obtained by polarimetric determination, and the results of a similar comparison, carried out on the mixed bases regenerated from the tartrate precipitates from the three quinetums are given in Table II. There is some doubt as to what figures should be taken for the rotations of quinine and cinchonidine bases: thus Rabe⁵ gives -158° for quinine and -111° for cinchonidine. For the present purpose -172° has been taken for anhydrous quinine, calculated from Howard and Chick's statement⁶ that quinine trihydrate has $[\alpha]_D^{15^\circ C.} = -145.2^\circ + 0.657 c$, c being the concentration in 97 per cent. alcohol of the solution used for the observation. The figure for anhydrous cinchonidine is arrived at from the similar formula⁶ $[\alpha]_D^{15^\circ C.} = -107.48^\circ + 0.3 c$ and is taken as -108.4° .

TABLE II

No. of sample	Methoxyl found per cent.	Calculated from methoxyl determination.		[α] _D	
		Quinine per cent.	Cinchonidine per cent.	Found	Calculated
1	4.45	46.55	53.45	-124.7°	-138°
2	3.99	41.77	58.23	-126.5°	-135°
3	5.50	57.55	42.45	-132.1°	-145°

It will be noticed that in every case the specific rotation found is markedly lower than that calculated from the composition as determined by determination of methoxyl. It was suggested in the previous paper that this discrepancy is due to the precipitation of cinchonine along with the quinine and cinchonidine. Cinchonine being dextrorotatory ($[\alpha]_D = +226.5^\circ$) has a far greater effect on the rotation than it has upon the methoxyl determination, and so figures for quinine obtained by the polarimetric method are likely to be understated, the inherent defects of the tartrate precipitation method being accentuated. In order to obtain evidence on this point, 10 grammes each of commercial quinine base (corresponding to 9.191 grammes of anhydrous base) and commercial cinchonine (corresponding to 9.972 gms. of anhydrous base) were dissolved in 44 c.c. of 10 per cent. hydrochloric acid and the solution diluted to 1000 c.c. Of this solution equal aliquot parts were brought to pH 4.2, 4.5, 5.0, 5.2 and 6.2 respectively, by the addition of dilute sodium hydroxide. To 100 c.c. of each of these "neutralised" fractions 10 grammes of sodium potassium tartrate dissolved in 15 c.c.

of hot water was added. After standing overnight the precipitates were collected, washed with a little water and dried at 110° C. A correction of 0.0008 gm. for each c.c. of filtrate and washings was added to the weight thus obtained. The results of the experiments carried out with these precipitates are given in Table III, in which the weights are in grammes throughout.

TABLE III

<i>p</i> H value of solution used	4.2	4.5	5.0	5.2	6.2	Calculated for original solution
Wt. of tartrate ppt. ..	15.32	12.14	12.21	12.32	14.11	—
Wt. of tartrate ppt. × 0.7941 = quinine base	12.17	9.64	9.70	9.79	11.20	—
Wt. of quinine recovered from tartrate ppt. ..	9.39	9.70	9.53	9.61	11.38	9.19
Wt. of cinchonine recovered from filtrate	9.56	9.53	9.75	9.49	7.74	9.97
Quinine + cinchonine recovered	18.95	19.23	19.28	19.10	19.12	19.16
Characters of recovered quinine						Original quinine used
Methoxyl found, per cent.	8.99	8.90	8.97	8.97	7.66	9.15
Specific rotation $[\alpha]_D$	-156.0°	-155.4°	-154.6°	-155.6°	-95.6°	-162.4°

The precipitates are quite similar in character when formed in solutions of *p*H 4.5, 5.0 and 5.2, but differences appear in solutions at either end of this range. In the solution of *p*H 4.2 too much tartrate was apparently precipitated, but the quinine actually recovered from this precipitate was about the same in weight and character as that from the next three solutions, and the excess weight of the original tartrate precipitate in this instance is due to the formation of the sparingly soluble potassium hydrogen tartrate, which is carried down with the alkaloidal tartrate. In the solution of *p*H 6.2 the deficiency in the recovery of cinchonine from the filtrate, the large amount of base recovered from the tartrate precipitate, and the low methoxyl and low specific rotation of this recovered base all clearly indicate that the tartrate precipitate contained cinchonine, and the agreement between the amount of base found and calculated for the tartrate precipitate indicates that the cinchonine is precipitated as tartrate and not as base. It is unfortunately

impossible to calculate accurately from either the methoxyl figures or the specific rotations the amount of cinchonine tartrate precipitated from each of these solutions because the commercial quinine used contained cinchonidine and hydroquinine, and the cinchonine contained hydrocinchonine, but assuming, what is probably the case, that these hydro-bases remained with their respective parent alkaloids during the various operations, and taking the following values of $[\alpha]_D$ for the three bases: quinine -172.0° , cinchonidine, -108.4° , cinchonine $+226.5^\circ$, the following values can be calculated from the methoxyl determinations and the observed specific rotations:—

TABLE IV

	Calculated percentages of		
	Quinine	Cinchonidine	Cinchonine
Quinine, as used	95.66	2.30	2.04
Ppt. from solution pH 4.2	94.02	2.34	3.64
" " pH 4.5	93.05	3.29	3.66
" " pH 5.0	93.79	2.19	4.02
" " pH 5.2	93.79	2.49	3.72
" " pH 6.2	80.06	1.03	18.91

It should be clearly understood that there is little or no cinchonine in commercial quinine, and the apparent cinchonine in the quinine used is probably due to defects in our knowledge of the specific rotations of the pure cinchona alkaloids. But it may be assumed that the excess above 2.04 recorded in the remaining lines of the table does in reality indicate the presence of some cinchonine in the precipitated tartrates. The practical point that emerges from these results is that the solution from which the quinine and cinchonidine tartrates are precipitated should be faintly acid to ensure a minimum precipitation of cinchonine tartrate, and that if this tartrate precipitate is to be used for polarimetric determination of quinine and cinchonidine it should be reprecipitated to remove as much cinchonine tartrate as possible (see below). The importance of this point is obvious when it is remembered that each unit per cent. of cinchonine base, in the regenerated bases, lowers the percentage of quinine base, calculated from a polarimetric determination, by 5.27.

In the previous paper dealing with *Cinchona febrifuge*³ it was pointed out that the cinchonine obtained by Chick's method was impure. That difficulty is due to the large amount of amorphous alkaloids, sparingly soluble in ether present in such crude preparations as the cinchona febrifuges of the present day,

and has not been met with to anything like the same extent in the course of the present work. It has, however, been observed that when much quinidine is present in quinetum, some of it is carried down with the cinchonine and can be recovered by crystallising the crude cinchonine from alcohol and determining the quinidine in the alcoholic mother liquors.

Using the data recorded above, quinetum samples 2 and 3 already mentioned were re-examined along with two other products, (A) an artificial mixture of commercial cinchona alkaloids made up as follows: quinine 20; cinchonidine 20; quinidine 10; cinchonine 50 per cent., and (B) a specially prepared sample of the total alkaloids of the bark of *Cinchona succirubra*.

Chick's process of analysis was used with the following additions and modifications:—

Quinine and Cinchonidine. These were precipitated together as tartrates, from a faintly acid solution, and after washing with 10 c.c. of water the precipitate was dried at 105°C., weighed, and the methoxyl content determined, the proportions of quinine being calculated on the assumption that the dried precipitate consists of quinine tartrate $(C_{20}H_{20}O_2N_2)_2$, $C_4H_6O_6$, H_2O yielding 7.59 per cent. of methoxyl and containing 79.41 per cent. of quinine, with cinchonidine tartrate $(C_{19}H_{22}ON_2)_2$, $C_4H_6O_6$ yielding no methoxyl and containing 79.68 per cent. of cinchonidine.

Polarimetric determinations were carried out on the mixed tartrate precipitate by Commelin's method,⁷ which appears to be extensively used on the Continent, though references to it in the literature of cinchona analysis are scanty.

The mixed tartrate precipitate was also reprecipitated once to remove any possible impurities such as cinchonine and amorphous alkaloids and the methoxyl and polarimetric estimations repeated.

Cinchonine and Quinidine. As already stated, the cinchonine isolated in these preparations, unlike that obtained from the cinchona febrifuges previously examined, was reasonably clean. It did, however, contain quinidine, which was recovered by boiling the crude cinchonine with 50 c.c. of alcohol, allowing the mixture to stand for several hours, filtering off the undissolved cinchonine and washing the latter with 20 c.c. of alcohol on the filter. The combined filtrate and washings were taken to dryness, the residue dissolved in 30 c.c. of 10 per cent. acetic acid and the quinidine determined as usual as hydriodide, the amount of quinidine base so found being deducted from the crude cinchonine and added to the quinidine already estimated in the original process.

The results obtained are recorded in Table V.

TABLE V

	Quinetum		Sample	Sample
	No. 2 per cent.	No. 3 per cent.	A per cent.	B per cent.
<i>Quinine</i> , methoxyl, crude tartrate.				
Analysis 1	17.89	15.32	20.67	29.3
Ditto Analysis 2	18.75	15.42	21.52	—
methoxyl, reprecipitated tartrate..	17.36	13.94	21.61	29.3
by polarimetric determination, crude tartrate	11.95	} too dark	18.76	25.4
by polarimetric determination, reprecipitated tartrate	15.68		20.88	27.0
<i>Cinchonidine</i> , methoxyl, crude tartrate				
(diff.) No. 1	27.46	13.21	21.54	24.3
Ditto (diff.) No. 2	25.91	12.98	20.67	—
methoxyl, recip. tartrate (diff.) ..	25.35	10.50	20.10	23.6
by polarimetric determination, crude tartrate	33.43	} too dark	23.46	28.2
Ditto reprecip. tartrate	27.03		20.83	25.9
<i>Cinchonine</i> . Analysis No. 1	46.43	39.00	49.10	24.7
" No. 2	45.84	37.50	49.55	—
<i>Quinidine</i> . Analysis No. 1	7.10	4.26	9.27	1.6
" No. 2	6.24	4.62	8.55	—
<i>Amorphous alkaloids</i> . Analysis No. 1	nil	17.09	nil	8.5
" No. 2	nil	16.86	nil	—
<i>Moisture</i>	1.00	1.70	0.90	5.9
<i>Ash</i>	4.60	1.80	0.16	0.16

Quinine and Cinchonidine. The agreement between the sum of these two bases in the duplicate analyses is satisfactory. The differences between quinine determined by (1) methoxyl and (2) polarimeter are now much less than in the previous series, especially when both are determined on the reprecipitated tartrate; this is no doubt mainly due to elimination of cinchonine, first by precipitation from a faintly acid instead of a neutral solution, and secondly by reprecipitation. The latter is clearly an important precaution, as indicated by the change in the polarimetric quinine figure before and after reprecipitation in the case of quinetum No. 2. The drop in the quinine by methoxyl, before and after reprecipitation in the case of quinetum No. 3 is undoubtedly due to the removal of amorphous alkaloids, which yield methoxyl, and it is unfortunate that in this case the tartrate precipitate was too dark coloured to permit of a polarimetric determination even after reprecipitation. It will be noticed that quinine by methoxyl is invariably higher than quinine by polarimeter. From all that is known of methoxyl determinations the authors are of opinion that quinine by methoxyl is probably still a little below the actual figure, and that

the low figures obtained for quinine by polarimeter are due (1) to the use of polarimetric constants for a quinine containing less hydroquinine than is normally present in the quinine found in natural mixtures of cinchona alkaloids or in such mixtures as these quinetum preparations, and (2) to the large effect of small errors of observation on the final calculated result for quinine and cinchonidine.

In Commelin's process for the polarimetric determination of quinine and cinchonidine the figures in the tables used correspond to the following observed rotations for quinine and cinchonidine tartrates:—

Quinine tartrate, $(C_{20}H_{24}O_2N_2)_2, C_4H_4O_6, H_2O$ dried at $105^\circ C$, is the monohydrate and has rotation -8.85° .

Cinchonidine tartrate, $(C_{19}H_{22}ON_2)_2, C_4H_4O_6$, dried at $105^\circ C$. is anhydrous and has rotation -5.48° .

These figures have been checked for the present investigation by using specially purified quinine and cinchonidine tartrates.

The quinine tartrate was made from a specimen of quinine acid sulphate, which had been recrystallised from water five times. It then agreed in constants with the pure acid sulphate prepared by Tutin.⁸ Unfortunately no method has yet been published which permits of even approximately accurate estimation of the quantities of hydrogenated alkaloids found in association with the various cinchona alkaloids. In the present instance quantitative hydrogenation was used and this sample of purified quinine in two experiments absorbed 99.5 and 100.2 per cent. of the calculated amount of hydrogen required to convert it into hydroquinine.

The sample of cinchonidine used absorbed in two experiments 99 per cent. of the calculated amount of hydrogen.

The examination of the thoroughly air-dried tartrates made from these two specially purified specimens of quinine and cinchonidine gave the following results:—

	Loss in weight per cent.	α_D by Commelin process	Methoxyl per cent.	Anhydrous quinine tartrate calculated from methoxyl
<i>Quinine tartrate</i>				
air-dried	—	—	7.33	94.4
dried at $95^\circ C$. <i>in vacuo</i> ..	1.38	—	7.40	95.3
” $110^\circ C$. atmos. pressure	1.69	-8.85°	7.48	96.2
” $125-130^\circ C$. <i>in vacuo</i>	3.66*	-9.00°	7.62	98.0
<i>Cinchonidine tartrate</i>				
air-dried	—	-5.26°	nil	nil
dried at $95^\circ C$. atmos. pressure	0.38	-5.30°	—	—
” $110^\circ C$. ” ..	4.31	-5.49°	—	—
” $125-130^\circ C$. <i>in vacuo</i> ..	4.48†	—	—	—

* Calc. for $2H_2O$, 4.32 per cent. † Calc. for $2H_2O$, 4.65 per cent.

It is clear from these results that the figures for the rotation of quinine and cinchonidine used in the Commelin process are those of the pure or nearly pure bases, whereas the quinine and the cinchonidine to be estimated in such mixtures as those now being dealt with contain considerable quantities of the corresponding hydro-bases with lower rotations. Good quality commercial quinine sulphate, for example, only requires 97.5 per cent. of the calculated quantity of hydrogen to completely hydrogenate it, corresponding to the presence of at least 2.5 per cent. of hydroquinine in the commercial product. This associated hydroquinine lowers the rotation, and is therefore calculated as cinchonidine in the polarimetric determination. In the methoxyl determination, on the contrary, the hydroquinine appears as quinine which, for practical purposes, is its correct allocation.

Cinchonine. The "cinchonines" obtained in the preliminary analyses recorded in Table I were examined and gave the following results :—

TABLE VI

Source of Cinchonine	M.pt.	$[\alpha]_D^{25}$	Methoxyl per cent.	Fractions on recrystallisation	
				M.pt. above 253° C. per cent.	M.pt. 235° or less per cent.
Quinetum 1	252° C.	+181.7	0.98	73.11	12.46
" 2 ..	248° C.	+208.7	1.64	77.93	11.43
" 3 ..	240° C.	+210.4	1.91	67.86	25.23

The cinchonines from quinetums 1 and 2 contained 7.47 and 5.92 per cent. of matter (chiefly inorganic) insoluble in boiling alcohol. From the foregoing results the necessity of examining cinchonine precipitates as suggested in the previous paper³ is obvious. The figures for cinchonine in Table V have been corrected for included quinidine as already indicated and for inorganic matter where found, and are in reasonably good agreement in the duplicate analyses.

Quinidine. The hydriodide precipitates were satisfactory, as regards melting-point and rotation, from all three samples of quinetum. The figures given in Table V are corrected by methoxyl determinations and by addition of quinidine recovered from the crude cinchonine.

For the reasons given already the authors regard the quinine determined by methoxyl on the reprecipitated tartrate as the

most satisfactory figure, and the following final values for the composition of the five preparations examined may now be given.

TABLE VII

	Quinetum					Prep.	Prep.
	1 Per cent.	2 Per cent.	2 (Corr)* Per cent.	3 Per cent.	3 (Corr)* Per cent.	A Per cent.	B Per cent.
Quinine	32.1	18.5	17.4	14.7	13.9	21.6	29.4
Cinchonidine	36.9	25.7	25.3	10.9	10.5	20.1	23.6
Quinidine	0.4	3.2	6.2	3.8	4.4	8.9	1.6
Cinchonine	30.9	48.9	46.1	44.7	38.2	49.3	24.7
Amorphous alkaloids	nil	nil	nil	12.7	16.9	nil	8.5
Moisture	0.7	1.0	1.0	1.7	1.7	0.90	5.8
Ash	1.0	4.6	4.6	1.8	1.8	0.16	0.16

* Mean of duplicate analyses, Table V.

These results indicate the variable character of modern quinetum. De Vrij's original quinetum is represented by preparation B, consisting of the total alkaloids of *Cinchona succirubra* bark, in which the crystalline alkaloids quinine, cinchonidine and cinchonine are present in approximately equal proportions. Quinetum No. 1 clearly represents a similar preparation without the amorphous alkaloids, and it conforms with the definition of "quinetum" suggested recently by the Malaria Commission of the League of Nations.⁹

Quinetum No. 2 and preparation B. would come within the definition of the new mixture of cinchona alkaloids for which the Malaria Commission of the League of Nations⁹ has proposed the name "totaquina" and which must contain as a minimum 15 per cent. of quinine and 70 per cent. of crystallisable cinchona alkaloids and not more than 20 per cent. of amorphous alkaloids, 5 per cent. of ash and 5 per cent. of moisture. Quinetum No. 3 is just below the "totaquina" standard in quinine, and a little below it in crystallisable cinchona alkaloids. Preparation A. is, as already stated, not a commercial product, but merely a laboratory mixture of quinine 20, cinchonidine 20, quinidine 10 and cinchonine 50 per cent. used as an approximate guide to the accuracy of this method of examining mixtures of cinchona alkaloids. The differences between the proportions of these alkaloids used and those found are due (1) to the fact that commercial cinchona alkaloids are not pure and (2) to experimental error. It is interesting to note that preparation B, representing the total alkaloids of *Cinchona succirubra* bark, contains 1.6 per cent. of quinidine, indicating that the bark used must have included some root bark as the stem bark of this species does not contain quinidine.

SUMMARY

It is shown that "quinetum," originally defined as the total alkaloids of "red cinchona bark," though still manufactured and used in small quantities, has changed considerably in character and is now of variable composition. Of three samples examined, only one meets the new specification suggested recently by the Malaria Commission of the League of Nations. The other two are to be regarded as "totaquinas," though one of them is a little below the standard suggested by the same authority for that product.

It is shown that the discrepancy previously noted between "quinine and cinchonidine" determined (a) by the methoxyl method, (b) by the polarimetric method, in mixtures of cinchona alkaloids is due to inclusion of cinchonine tartrate in the initial precipitation of quinine and cinchonidine tartrates, and can be avoided by (1) precipitation of the tartrates from slightly acid solutions and (2) reprecipitation of the tartrates prior to taking polarimetric readings.

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